REMARKS/ARGUMENTS

Pursuant to RCE and Amendment filed 10/4/2004, claims 1, 3, 5-7, 9-18, 24, 28-33, and 47-50 were pending. The Non-final Office Action dated 11/10/2004 rejected claims 1, 3, 5-7, 9-10, 12-13, 24, 28 29-31, 32, 33, 47-50; claims 1, 5, 11, and 16-18 were objected to. In view of the present amendment, claims 1, 3, 6, 9, 11-18, 24, 28-32 and 47-51 are currently pending.

Claim Amendments

Claim 1 has been amended to recite steps of removing a culture medium excess agent and adding a pharmaceutically acceptable excipient. Support for this step may be found, for example in Example 1, paragraph 00243, where the bacterial strains tested were washed, concentrated and resuspended in Na_2HPO_4. With regard to the amendatory phrase "pharmaceutically acceptable excipient," this term is discussed at page 39, paragraph 00152 of the specification. The specification there makes clear that the term is being used in its art-accepted sense, and is not to be equated with any material that can act as a diluent. In other words, the "pharmaceutically acceptable excipient" must be "pharmaceutically acceptable," i.e. non-toxic and biologically acceptable in the recipient.

With regard to claim 1 and 24, support for the amendatory language "vaccine" is found throughout the specification. "Vaccine" is defined at paragraph [00127]. See also paragraphs [00142] and [00149]. With regard to the amendatory language "avirulent due to having therein an alteration in a *dam* gene," in claim 24, a discussion of the fact that the present dam mutants are unable to cause disease but are able to elicit a fully protective immune response is found at paragraph [00274] of the present specification.

For the convenience of the Examiner, paragraphs of the Detailed Action are set forth and responded to in the same order as presented in the Office Action.

Allowable Subject Matter **(Office Action Paragraph 2)**

Applicants note with appreciation the indication of allowability of claims 11 and 16-18 if rewritten in independent form. Claim 11 is currently dependent from claim1, reciting a method of preparing a composition and is limited to certain species of bacteria. Claim 1 believed to be in allowable form for reasons discussed below.

Claim Objections **(Office Action Paragraphs 2-4)**

A misspelling in claim 1 was pointed out.

Claim 5 was objected to as broadening the scope of claim 1 in that claim 5 requires expressing methyltransferase and claim 1 defines the agent that "prevents" the bacteria's *dam* gene expression.

Response

The misspelling in claim 1 has been corrected.

Claim 5 has been cancelled. New claim 51 contains the subject matter of claim 5 in independent form. Cross protection elicited by both a Dam- and a Dam overproducing strain is described in Example 3 of the present specification. See also paragraph 00260 discussing the effects of Dam overproduction.

Rejection of Claim 5 under 35 USC § 112 (Office Action Paragraph 5)

Claim 5 was rejected as indefinite in that claims 5 and 7 recite a combination of claim limitations that are not internally consistent.

Response

Claim 5 has been rewritten in independent form.

Rejection of Claims 1,3, 5-7, 9-10, 12-13, 47-48 under 35 USC §102(b) over Torreblanca et al (Office Action Paragraph 7)

Torreblanca et al. were said to disclose a method of making a composition having reduced bacterial virulence comprising the steps of providing a virulent bacteria having a DNA methyl transferase activity and contacting the bacteria with an agent that prevents the bacteria's *dam* gene expression by altering the bacteria's native level of methylation.

Response

This rejection is respectfully traversed. The reference does not disclose a number of recited elements of the rejected claims. "A rejection for anticipation under section 102 requires that four corners of a single prior art document describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice invention without undue experimentation." In re Paulsen, 30 3d 1475, 1478-79, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994)." Ex Parte Parks, USPTO Board of Patent Appeals and Interferences Appeal No. 2004-0334.

Claim preambles must also be considered in claim interpretation and may be construed as limiting the claim scope. Invitrogen Corp. v. Biocrest Mfg., L.P., 327 F.3d 1364, 1369, 66 USPQ2d 1631, 1634 (Fed. Cir. 2003).

With regard to claim 1, Torreblanca et al. do not disclose or suggest a method of preparing a **vaccine having reduced bacterial virulence**; **separating** the bacteria from its culture medium and any agent therein; or adding to it a pharmaceutically acceptable **excipient**.

With regard to claim 48, Torreblanca et al. do not disclose or suggest a method of treating a pathogenic bacterial infection; or administering to a subject infected with

the pathogenic bacteria a therapeutically effective amount of a vaccine preparation.

Torreblanca et al. do not suggest that the Dam- mutants used in their study are avirulent and, therefore suitable for use as a vaccine. They do not disclose or suggest any use for these compositions apart from use in their studies. They do not suggest preparing a therapeutic composition of any kind. With regard to claim 9, they do not disclose the use of an agent that binds a native *dam* nucleic acid sequence. The authors use random transposon insertion and isolate *dam*- mutants. Such mutants may or may not have other, pharmaceutically deleterious, mutations. Furthermore, they do not disclose even a preparation of the altered bacteria, since the mutants are isolated by plating on solid media.

Rejection of Claims 1, 12, 13, 24, 29-31 under 35 USC §102(e) over Kelanthous et al. US 6,585,975 (Office Action Paragraph 8)

Kleanthous et al. was cited as disclosing a method of making a composition having reduced bacterial virulence of a pathogenic bacteria.

Response

This rejection is respectfully traversed. **The reference relies on a priority document that lacks any disclosure relevant to the present claims.**

The present application related back to applications having priority dates of Feb. 2 1999 and May 5, 1999. Support for the present claims may be found in those documents, as follows: The priority application Ser. No. 60/198,250, converted from 09/305,603, both having a filing date of 5/5/99 contains a description of experiments immunizing mice with a S. typhimurium preparation that could serve as a live attenuated vaccine is found at pp. 22-23. Discussion of the use of physiologically acceptable base or dispersion may be found at p. 35. Page 23 contains an explanation of the inventors' finding that a *dam* mutant is an effective vaccine because it is totally attenuated yet provides full protection against

challenges with wild-type, virulent bacteria.

The cited Kleanthous patent application was not filed until Nov. 1, 1999.

A review of the Kleanthous et al. priority document, PCT/US98/08890, filed 4/30/98, entitled "Anti Helicobacter vaccine composition for use by the subdiaphragmatic system route, and combined mucosal/parental immunization method," shows that it does not disclose attenuated *S. typhimurium,* as cited by the Examiner. The PCT publication is directed to the manufacture of a pharmaceutical composition derived from *Helicobacter* and intended to treat a *Helicobacter* infection.

Furthermore, even if the Kleanthous et al. patent 6,585,975 was available as a reference, it does not enable the preparation of *dam-* Salmonella vectors. The patent makes only a passing reference to their possible existence at Col. 3, l. 7.

Rejection of Claims 1, 5-7, 9-10, 12, 14, 15, 47 and 49 and 7 under 35 USC §102(b) over Bandyopadhyay et al. (Office Action Paragraph 9)

Bandyopadhyay et al. is cited as disclosing a composition that is immunogenic, comprising "a diluent (a species of the instantly claimed excipients), specifically minimal media containing 1% casamino acids (see page 69, col.2, fig. 3 legend narrative)"

Response

This rejection is respectfully traversed. Bandyopadhyay et al. disclose the cloning of the *Vibrio cholerae dam* gene. **There is no disclosure or suggestion of preparing any composition for a specific use. There is no disclosure or suggestion of preparing a therapeutic composition or a method of treatment as presently claimed. One cannot equate growing bacteria in culture with the recited method of preparing a therapeutic composition.**

Bandyopadhyay et al. disclose the cloning and characterization of the *dam* gene of *Vibrio cholerae.* As part of their studies, the authors transformed known E. coli *dam*- strain GW3810 (isolated in prior work by others from transposon mutagenesis). The cloned *Vibrio cholerae dam* gene, contained on plasmids introduced into the E. coli strain, was found to complement the missing *dam* gene product. Fig. 3 legend describes the preparation of the ^{35}S labeled V. cholerae Dam protein. The E. coli host cells containing the V. cholerae plasmid were grown in minimal media, irradiated with uv light (to induce Dam expression, and further incubated. Then, 200 μg of D-cycloserine was added. D-cycloserine is an antibiotic which inhibits cell wall synthesis. The cells were then harvested, suspended in fresh sulfur-depleted medium, incubated and the proteins were labeled with ^{35}S labeled methionine. The cells were then harvested, washed and lysed for gel analysis.

Bandyopadhyay et al. give no suggestion of, or reason for preparing a therapeutic composition, as evidenced by the use of antibiotics and radioactive materials. The step of adding a "pharmaceutically acceptable excipient" is simply not present, suggested, or workable with the procedures and preparations described in this reference. The specification does not define pharmaceutically acceptable excipients to include any diluent. It simply states, as is common knowledge, that certain acceptable excipients may act as diluents. See paragraph 00152, "For example, an excipients can give form or consistency to the vaccine composition, or act as a diluent." Antibiotics and radioactive materials are not pharmaceutically acceptable excipients, and they would have to be separated from the medium according to the presently recited method of claim 1. Such separation is neither disclosed nor suggested by Bandyopadhyay et al.

Rejection of claims 3, 5-7, 28, 32-33, and 48-50 under 35 USC § 103(a) over Kleanthous et al. in view of Torreblanca et al. (Office Action Paragraphs 10-11)

The rejection states that Kleanthous et al. as teaches an attenuated strain of

Salmonella with an inactivated *dam* gene and a method of inducing an immune response, but fails to show inactivation of the *dam* gene by genetic means. Torreblanca is said to show the production of recombinant Salmonella strains that evidence inactivated *dam* genes utilizing genetic means (table 1). It is stated that "Kleanthous et al. and Torreblanca et al. produce attenuated strains if Salmonella with inactivated *dam* genes, and Torreblanca et al. disclose a plurality of genetic means.

Response

As discussed above, **the Kleanthous et al. patent is not citable in this case due to its later filing date.** The priority document to Kleanthous et al. does not disclose the use of Salmonella vectors for vaccination. Torreblanca et al. does show the isolation of *dam*-mutants, albeit by random transposon mutagenesis. Neither reference discloses or suggests the preparation of a therapeutic composition, nor would such be inherent in the combination. Torreblanca et al. make no inquiry into the virulence of the numerous strains that they created and used.

Method of Treatment Claims

The rejection of the method of treatment claims 24, 28-32 and 48-50 deserves separate discussion. The present claims may be regarded as generally including claims to methods of preparing a therapeutic composition and methods of treating a bacterial infection (e.g. independent claims 24 and 32). Claim 24 is rejected under Office Action Paragraph 8 as anticipated by Kleanthous as evidenced by Torreblanca. Claim 32 is rejected under Office Action paragraph 10 as obvious over Kleanthous et al. in view of Torreblanca et al.

As stated above, the effective date of Kleanthous et al. for purposes of suggesting the use of a *dam*-altered (claim 24) or *dam* deleted bacteria is after Applicant's priority date. There is nothing in the art of record to suggest Applicants' finding, as reported in

Science, that the *dam* gene may be modulated to affect the virulence of a pathogenic bacteria. This is particularly unexpected in view of the gene expression of many pathogenic bacteria, which differs between in vitro growth and in vivo growth. See the discussion at paragraph 00270. Thus, the finding that *dam*- bacteria have immunogenic protective effects, yet do not cause harmful infection, and are therefore useful in methods of treatment has not been addressed at all by the prior art of record. The recited methods also involve unexpected results in that the present methods of treatment are effective in treating species other than the species of bacteria administered (See paragraph 00116).

Conclusion

Applicants request that this amendment to the claims and specification be entered and the rejections of claims 1, 3, 6, 9, 11-18, 24, 28-32 and 47-51 be withdrawn. It is believed that the present Amendment places the application in condition for allowance. The allowance of currently pending claims 1, 3, 6, 9, 11-18, 24, 28-32 and 47-51, as well as the timely issuance of a Notice of Allowance is earnestly solicited. The Examiner may call Applicants' attorney at the number below in the event that a telephone conference would expedite prosecution of the present case.

Respectfully submitted,

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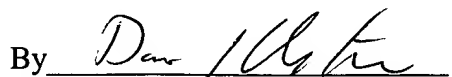
By 
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